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(54) Title: NOVEL CRYSTAL FORMS OF ATORVASTATIN HEMI-CALCIUM AND PROCESSES FOR THEIR PREPARATION, AS WELL AS NOVEL PROCESSES FOR PREPARING ATORVASTATIN HEMI-CALCIUM FORMS I, VIII AND IX

(57) Abstract: The present invention provides novel forms of atorvastatin designated Forms IXa, XIV, XVI and XVII and novel processes for their preparation as well as processes for preparing atorvastatin hemi-calcium Forms I, XIII and IX.

NOVEL CRYSTAL FORMS OF ATORVASTATIN HEMI-CALCIUM AND PROCESSES FOR THEIR PREPARATION, AS WELL AS NOVEL PROCESSES FOR PREPARING ATORVASTATIN HEMI-CALCIUM FORMS I, VIII AND IX

CROSS-REFERENCE TO RELATED APPLICATIONS

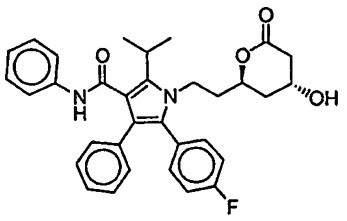
This application claims benefit of U.S. provisional applications Serial Numbers 60/357,181, filed February 15, 2002 and 60/425,325, filed November 12, 2002, both of which are incorporated herein by reference.

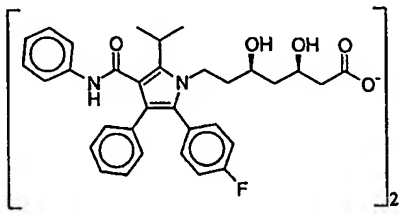
FIELD OF THE INVENTION

The present invention relates to crystalline polymorphic forms of atorvastatin hemi-calcium and novel processes for preparing crystalline forms of atorvastatin hemi-calcium.

BACKGROUND OF THE INVENTION

Atorvastatin, ([R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid), depicted in lactone form in formula (I) and its calcium salt of formula (II) are well known in the art, and described, *inter alia*, in U.S. Patents Nos. 4,681,893, 5,273,995, and in copending USSN 60/166,153, filed November 17, 2000, all of which are herein incorporated by reference.

(I) 

 (II)

Processes for preparing atorvastatin and its hemi-calcium salt are also disclosed in U.S. Patent Application Publication No. 2002/0099224; U.S. Patents Nos. 5,273,995; 5,298,627; 5,003,080; 5,097,045; 5,124,482; 5,149,837; 5,216,174; 5,245,047, 5,280,126; Baumann, K.L. et al. *Tet. Lett.* 1992, *33*, 2283-2284., which are hereby incorporated by reference in their entirety and in particular for their teachings related to the preparation of atorvastatin and atorvastatin hemi-calcium.

Atorvastatin is a member of the class of drugs called statins. Statin drugs are currently the most therapeutically effective drugs available for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. A high level of LDL in the bloodstream has been linked to the formation of coronary lesions which obstruct the flow of blood and can rupture and promote thrombosis. Goodman and Gilman, *The Pharmacological Basis of Therapeutics* 879 (9th ed. 1996). Reducing plasma LDL levels has been shown to reduce the risk of clinical events in patients with cardiovascular disease and patients who are free of cardiovascular disease but who have hypercholesterolemia. Scandinavian Simvastatin Survival Study Group, 1994; Lipid Research Clinics Program, 1984a, 1984b.

The mechanism of action of statin drugs has been elucidated in some detail. They interfere with the synthesis of cholesterol and other sterols in the liver by competitively inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase enzyme ("HMG-CoA reductase"). HMG-CoA reductase catalyzes the conversion HMG to mevalonate, which is the rate determining step in the biosynthesis of cholesterol, and so, its inhibition leads to a reduction in the concentration of cholesterol in the liver. Very low density lipoprotein (VLDL) is the biological vehicle for transporting cholesterol and triglycerides from the liver to peripheral cells. VLDL is catabolized in the peripheral cells which releases fatty acids which may be stored in adopcytes or oxidized by muscle. The VLDL is converted to intermediate density lipoprotein (IDL), which is either removed by an LDL receptor, or is converted to LDL. Decreased production of cholesterol leads to an increase in the number of LDL receptors and corresponding reduction in the production of LDL particles by metabolism of IDL.

Atorvastatin hemi-calcium salt trihydrate is marketed under the name LIPITOR by Warner-Lambert Co. Atorvastatin was first disclosed to the public and claimed in U.S. Patent No. 4,681,893. The hemi-calcium salt depicted in formula (II) is disclosed in U.S. Patent No. 5,273,995. The '995 patent teaches that the hemi-calcium salt is obtained by crystallization from a brine solution resulting from the transposition of the sodium salt with $CaCl_2$ and further purified by recrystallization from a 5:3 mixture of ethyl acetate and hexane.

The present invention provides new crystal forms of atorvastatin hemi-calcium in both solvated and hydrated states. The occurrence of different crystal forms (polymorphism) is a property of some molecules and molecular complexes. A single molecule, like the atorvastatin in formula (I) or the salt complex of formula (II), may give rise to a variety of solids having distinct physical properties like melting point, X-ray diffraction pattern, infrared absorption fingerprint and NMR spectrum. The differences in the physical properties of polymorphs result from the orientation and intermolecular interactions of adjacent molecules (complexes) in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family. One of the most important physical properties of pharmaceutical polymorphs is their solubility in aqueous solution, particularly their solubility in the gastric juices of a patient. For example, where absorption through the gastrointestinal tract is slow, it is often desirable for a drug that is unstable to conditions in the patient's stomach or intestine to dissolve slowly so that it does not accumulate in a deleterious environment. On the other hand, where the effectiveness of a drug correlates with peak bloodstream levels of the drug, a property shared by statin drugs, and provided the drug is rapidly absorbed by the GI system, then a more rapidly dissolving form is likely to exhibit increased effectiveness over a comparable amount of a more slowly dissolving form.

Crystalline Forms I, II, III and IV of atorvastatin hemi-calcium are the subjects of U.S. Patents Nos. 5,959,156 and 6,121,461 assigned to Warner-Lambert and crystalline atorvastatin hemi-calcium Form V is disclosed in commonly-owned International Publication No. WO 01/36384 (PCT Application No. PCT/US00/31555). There is an assertion in the '156 patent that Form I possesses more favorable filtration and drying characteristics than the known amorphous form of atorvastatin hemi-calcium. According to the '156 patent, Form I is characterized by powder X-ray diffraction pattern having peaks at 9.150, 9.470, 10.266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734, 24.438, 28.915 and 29.234 degrees two-theta.

Commonly owned, co-pending U.S. Patent Application No. 2002/0115709 discloses atorvastatin hemi-calcium Form VII, processes for preparing it and pharmaceutical compositions containing it.

Commonly owned co-pending U.S. Patent Application No. 2002/0183378 discloses Forms VI, VIII, IX, X, XI and XII atorvastatin hemi-calcium, processes for preparing them and pharmaceutical compositions containing them.

According to the '378 publication, atorvastatin hemi-calcium Form VIII produces a powder X-ray diffraction pattern using conventional CuK_α radiation having peaks at 6.9, 9.3, 9.6, 16.3, 17.1, 19.2, 20.0, 21.6, 22.4, 23,9, 24.7, 25.6, and 26.5±0.2 degrees 2θ. Additional peaks have been observed at 4.8, 5.2, 5.9, 7.0, 8.0, 9.3, 9.6, 10.4, 11.9, 16.3, 17.1(broad), 17.9, 18.6, 19.2, 20.0, 20.8, 21.1, 21.6, 22.4, 22.8, 23.9, 24.7, 25.6, 26.5, 29.0± 0.2 degrees two-theta.

Synchrotron X-ray powder diffraction analysis was performed on Form VIII to determine its crystal system and unit cell dimensions. Form VIII was found to have a monoclinic unit cell with lattice dimensions: a = 18.55-18.7 Å, b = 5.52-5.53 Å, c = 31.0-31.2 Å and angle β between the a and c axes of 97.5-99.5°.

Atorvastatin hemi-calcium Form VIII produces a cross-polarization, magic angle spinning solid-state ^{13}C NMR spectrum with resonances at the following chemical shift positions:: 17.8, 20.0, 24.8, 25.2, 26.1, 40.3, 40.8, 41.5, 43.4, 44.1, 46.1, 70.8, 73.3, 114.1, 116.0, 119.5, 120.1, 121.8, 122.8, 126.6, 128.8, 129.2, 134.2 , 135.1, 137.0, 138.3, 139.8, 159.8, 166.4, 178.8, 186.5 ppm. Form VIII is characterized by a solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts differences between the lowest ppm resonance and other resonances: 2.2, 7.0, 7.4, 8.3, 22.5, 23.0, 23.7, 25.6, 26.3, 28.3, 53.0, 55.5, 96.3, 98.2, 101.7, 102.3, 104.0, 105.0, 108.8, 111.0, 111.4, 116.4, 117.3, 119.2, 120.5, 122.0, 142.0, 148.6, 161.0 and 168.7.

Atorvastatin hemi-calcium Form VIII can exist as an ethanol solvate containing up to about 3 % ethanol by weight. Samples of atorvastatin hemi-calcium Form VIII also can contain up to 7% water as determined by Karl Fisher analysis.

The '378 application teaches that atorvastatin hemi-calcium Form VIII may be obtained by slurrying atorvastatin hemi-calcium in a mixture of ethanol and water at elevated temperature, preferably about 78-80°C.

It also teaches that Form VIII may be obtained starting from Form V by treating Form V with a mixture of EtOH:H_2O, preferably in the ratio of about 5:1 at an elevated temperature below reflux, preferably 78-80°C. An especially preferred EtOH:H_2O mixture

for that process contains about 4 % by volume water in ethanol. During the heating, atorvastatin Form V gradually dissolves and at the point of 78-80°C turbidity, with or without seeding, is observed. At this point the suspension is immediately cooled to room temperature.

Yet further, the '378 publication teaches that Form VIII may be obtained by treating atorvastatin hemi-calcium in EtOH, preferably absolute EtOH, at elevated temperature, preferably boiling EtOH. Under these conditions, the atorvastatin dissolves and reprecipitates. MeOH may be added at reflux. Added MeOH may adversely affect the yield, but may improve the chemical purity of the product. Starting materials for preparing Form VIII by this process can be crystalline forms of atorvastatin hemi-calcium, preferably Forms I and V and mixtures thereof or amorphous atorvastatin hemi-calcium. The quantity of EtOH or mixture thereof with water is preferably in the range of from about 10 to about 100 ml g^{-1}, more preferably about 20 to about 80 ml g^{-1}.

Form VIII also may be prepared by suspending atorvastatin hemi-calcium in certain 1-butanol/water and ethanol/water mixtures for a period of time sufficient to cause the conversion of the atorvastatin hemi-calcium to Form VIII. 1-Butanol/water mixtures should contain about 20% 1-butanol by volume at elevated temperature, preferably at reflux temperature.

According to the '378 publication, atorvastatin hemi-calcium Form IX produces a powder X-ray diffraction pattern using conventional CuK_α radiation having peaks at 4.7, 5.2, 5.7, 7.0, 7.9, 9.4, 10.2, 12.0, 17.0, 17.4, 18.2, 19.1, 19.9, 21.4, 22.5, 23.5, 24.8 (broad), 26.1, 28.7, 30.0±0.2 degrees two-theta. The crystal system and unit cell dimension of Form IX were determined using synchrotron X-ray powder diffraction analysis. Form IX has a monoclinic crystal lattice with lattice dimensions: a = 18.75-18.85 Å, b = 5.525-5.54 Å, c= 30.9-31.15 Å and angle β between the a and c axes of 96.5-97.5°.

Atorvastatin hemi-calcium Form IX produces a cross-polarization, magic angle spinning solid-state ^{13}C NMR spectrum with resonances at the following chemical shift positions: 18.0, 20.4, 24.9, 26.1, 40.4, 46.4, 71.0, 73.4, 114.3, 116.0, 119.5, 120.2, 121.7, 122.8, 126.7, 128.6, 129.4, 134.3, 135.1, 136.8, 138.3, 139.4, 159.9, 166.3, 178.4, 186.6 ppm. Form IX is characterized by a solid-state ^{13}C nuclear resonance having the following chemical shifts differences between the lowest ppm resonance and other resonances: 2.4,

6.9, 8.1, 22.4, 28.4, 53.0, 55.4, 96.3, 98.0, 101.5, 102.2, 103.7, 104.8, 108.7, 110.6, 111.4, 116.3, 117.1, 118.8, 120.3, 121.4, 141.9, 148.3, 160.4, 168.6.

The '378 publication discloses that Form IX may be prepared by slurrying atorvastatin hemi-calcium in butanol and isolating Form IX by, for example, filtration or decantation of the butanol, preferably by filtration. Preferred temperature ranges for the slurrying are from 78°C to the reflux temperature of the solvent. Recovery of atorvastatin hemi-calcium salt from the slurry can be enhanced by addition of an anti-solvent to the slurry before isolating Form IX. Preferred anti-solvents include isopropanol and *n*-hexane. Starting materials for preparing Form IX by this process can be crystalline or amorphous atorvastatin hemi-calcium, preferably Forms I and V and mixtures thereof.

The '378 publication further teaches that Form IX may be prepared by suspending Form VIII in ethanol, preferably absolute ethanol, at room temperature for a period of time sufficient to convert form VIII to Form IX, which may range from a few hours to 24 hours and typically requires about 16 hours. Thereafter, Form IX is recovered from the suspension. Form IX also may be prepared by maintaining Form VIII under a humid atmosphere.

Yet further, the '378 patent teaches that Form IX also may be prepared by suspending atorvastatin hemi-calcium Form V in mixtures of 1-butanol and either ethanol or water at reflux temperature for a period of time sufficient to convert Form V into Form IX and recovering Form IX from the suspension. Preferably the mixtures contain about 50 volume percent of each component.

Although Form I remedies some of the deficiencies of the amorphous material in terms of manufacturability, there remains a need for yet further improvement in these properties as well as improvements in other properties such as flowability, vapor impermeability and solubility. Further, the discovery of new crystalline polymorphic forms of a drug enlarges the repertoire of materials that a formulation scientist has with which to design a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a characteristic powder X-ray diffraction pattern of atorvastatin hemi-calcium Form IX obtained using a conventional X-ray generator with a copper anode.

Fig. 2 is a characteristic powder X-ray diffraction pattern of atorvastatin hemi-calcium Form IXa obtained using a conventional X-ray generator with a copper anode.

Fig. 3 is a characteristic powder X-ray diffraction pattern of atorvastatin hemi-calcium Form XIV obtained using a conventional X-ray generator with a copper anode.

Fig. 4 is a characteristic powder X-ray diffraction pattern of atorvastatin hemi-calcium Form XVI obtained using a conventional X-ray generator with a copper anode.

Fig. 5 is a characteristic powder X-ray diffraction pattern of atorvastatin hemi-calcium Form XVII.

SUMMARY OF THE INVENTION

The present invention provides new solid crystalline forms of atorvastatin hemi-calcium, and solvates and hydrates thereof.

More particularly, the present invention provides novel solid crystalline atorvastatin hemi-calcium characterized by a powder X-ray diffraction pattern obtained using conventional CuK_{α} radiation having peaks at 9.3 and 9.5 ±0.2 degrees two-theta. In addition, small peaks are observed at15.7, 20.5, 21.1, 22.8, 23.8, 24.0, 25.3, 26.4, 26.8, 27.2, 29.2, 31.6±0.2 degrees two-theta.

In another aspect, the present invention provides novel solid crystalline atorvastatin hemi-calcium characterized by a powder X-ray diffraction pattern obtained using conventional CuK_{α} radiation having peaks at 7.6, 9.8, 16.5, 29.4 ± 0.2 degrees two-theta and novel processes for its preparation.

In another aspect, the present invention provides a novel crystalline form of atorvastatin hemi-calcium characterized by a powder X-ray diffraction pattern obtained using conventional CuK_{α} radiation having peaks at 16.5, 21.9, 29.5 ± 0.2 degrees two-theta and novel processes for its preparation.

In another aspect, the present invention provides a novel crystalline form of atorvastatin hemi-calcium characterized by a powder X-ray diffraction pattern obtained using conventional CuK_{α} radiation by typical X-Ray peaks at 7.8, 9.5, 10.2, 18.2, 19.1, 25.3, 26.2, 30.1±0.2 degrees two-theta and novel processes for its preparation.

In another aspect, the present invention provides a novel process for preparing atorvastatin hemi-calcium Form VIII.

In another aspect, the present invention provides a novel process for preparing atorvastatin hemi-calcium Form IX.

In another aspect, the invention provides compositions and dosage forms comprising the novel solid crystalline atorvastatin hemi-calcium and their mixtures along with a pharmaceutically acceptable carrier, as well as methods of treating hyperlipidemia with the new forms.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Some crystalline forms of atorvastatin hemi-calcium of the present invention exist in a solvated state and hydrated state. Hydrates have been analyzed by Karl-Fisher and thermogravimetric analysis.

Powder X-ray diffraction ("PXRD") analysis employing conventional CuK_α radiation was performed by methods known in the art using a SCINTAG powder X-ray diffractometer model X'TRA equipped with a solid-state detector. Copper radiation of λ = 1.5418 Å was used. Measurement range: 2-40 degrees 2θ. The sample was introduced using a round standard aluminum sample holder with round zero background quartz plate in the bottom. Powdered samples were gently ground and filled in the round cavity of the sample holder by pressing with a glass plate.

As previously discussed, commonly assigned, co-pending U.S. Patent Application Publication No. 2002/0183378 teaches that atorvastatin hemi-calcium Form IX can be produced using mixtures of 1-butanol and either ethanol or water. It has now been found that suspending atorvastatin hemi-calcium Form V in mixtures of 1-butanol and water, wherein one or the other diluent is predominant in the mixture, will yield a more highly pure and crystalline atorvastatin hemi-calcium product. This product has been denominated Form IXa. Atorvastatin hemi-calcium Form IXa is characterized by its PXRD pattern (Fig. 2), which is similar in some respects to that of Form IX described in the '378 publication whose PXRD pattern is reproduced here as Fig. 1. However, there are differences between the two patterns. The most predominant difference is at about 9.5 degrees two-theta. There, a single strong peak is observed in the PXRD pattern of Form

IX whereas two strong peaks are observed 9.3 and 9.5 degrees two-theta in the Form IXa pattern. In addition, there are small peaks at 15.7, 20.5, 21.1, 22.8, 23.8, 24.0, 25.3, 26.4, 26.8, 27.2, 29.2 and 31.6±0.2 degrees two-theta in the PXRD pattern of Form IXa.

Atorvastatin hemi-calcium Form IXa is considered to be an especially crystalline, filterable and pure material having similar internal structure to Form IX, hence the designation Form IXa. Form IXa can be prepared by suspending atorvastatin hemi-calcium Form V in mixtures of 1-butanol and water in which either the 1-butanol or water constitutes from about 85% to about 95%, more preferably about 90%, of the mixture. The suspension can be heated to accelerate conversion of Form V to Form IXa. Sixteen hours at about 85°C is generally sufficient. Under these conditions, yields as high as 95% can be obtained and the impurity level of the material can be significantly reduced. The impurity content of the starting atorvastatin hemi-calcium can be reduced by about 50% or more. For example, Form IX can be obtained in about 0.7% chemical purity when starting with Form V of about 1.3% chemical purity. Chemical purity was measured by high performance liquid chromatography ("HPLC"). HPLC was performed on a Spherisorb® S5, C8 column, 250x4.6 mm with gradient elution: Solvent A 0.05M KH_3PO_4 adjusted to pH 5 with 1N KOH:acetonitrile: methanol:THF (62:26:8:4); Solvent B: methanol. The HPLC system was equipped with Waters® pumps and a UV detector set to detect at 254 nm.

Among the specific procedures that can be used, there may be mentioned the following. Form V is suspended in a mixture of 90% 1-butanol and 10% water (v/v). The mixture is used in an amount of about 20 milliliters per gram of Form V. The suspension is refluxed at 90°C for about 16 hours, after which time Form V is transformed into Form IX, which is then be recovered from the suspension by conventional means, like filtration.

According to another specific procedure, Form V is suspended in a mixture of 10% 1-butanol and 90% water (v/v). The mixture is used in an amount of about 20 milliliters per gram of Form V. The suspension is refluxed for about 16 hours, after which time Form V is transformed into Form IX, which is then recovered by conventional means.

The present invention further provides a novel polymorph of atorvastatin hemi-calcium that has been denominated Form XIV. Atorvastatin hemi-calcium Form XIV is characterized by a powder X-ray diffraction pattern obtained using conventional CuK_α

radiation (FIG. 3) having peaks at 7.6, 9.8, 16.5, 18.1, 20.0, 20.4, 21.9, 22.4, 23.6, 29.4 ± 0.2 degrees two-theta. The most characteristic peaks are those at 7.6, 9.8, 16.5, 29.4 ± 0.2 degrees two-theta.

In general terms, Form XIV can be obtained from a suspension of atorvastatin hemi-calcium in water. According to U.S. Patent No. 5,969,156, atorvastatin hemi-calcium Form I precipitates when calcium acetate is added to a solution of atorvastatin sodium in water. It is also said that Form I can be prepared by suspending amorphous atorvastatin hemi-calcium in water. In the specific example provided, Example 1, a mixture formed from atorvastatin sodium and calcium acetate in water was seeded with Form I shortly after addition of the calcium acetate solution and, thereafter, Form I was obtained.

We have found that suspending atorvastatin hemi-calcium in or precipitating atorvastatin hemi-calcium from water does not invariably lead to the production of Form I as might be expected after studying the '156 patent. On the contrary, in our hands, suspensions of atorvastatin hemi-calcium in water yield a previously unknown polymorph that we have denominated Form XIV. Form XIV is readily distinguishable from Form I (which is also obtained by precipitation from water, but with seeding with Form I) by the peaks at 7.6, 16.5, 20.0 and 19.4 degrees two-theta, which peaks are absent from the PXRD pattern of Form I.

It should be noted that in Example 3, below, the suspension is not stirred or seeded with a crystal of Form I. Atorvastatin hemi-calcium Form XIV can be prepared by suspending atorvastatin hemi-calcium in water until a fine suspension forms and then allowing the suspension to stand undisturbed until the fine crystals transform substantially into white flakes. The flakes can be separated from the suspension by conventional means, like decanting or filtering (either with or without suction and they do not clog the filter) and washing the crystals. The crystals of the fine suspension are very small giving the suspension the appearance of an emulsion. The transformation from fine suspension to flakes is readily apparent from visual inspection of the suspension. Preferred process parameters are as follows. The preferred starting material is atorvastatin hemi-calcium Form V. The fine suspension typically forms over a period of from about 2 to about 10 hours, on average about 5 hours. The fine suspension transforms into white flakes over

about one to about five days, with longer time periods being preferred for more complete conversion and a more easily filterable product. Other conditions which lead to the production of Form XIV may be discovered but presently the best method known is by suspending atorvastatin hemi-calcium in water that is not agitated and has not been seeded with a different polymorph of atorvastatin. Form XIV has been obtained in our laboratory without seeding of any kind.

Form XIV crystals can be transformed into another crystal form without contact with solvent. This new form has been denominated Form XVI. Form XVI is characterized by a powder X-ray diffraction pattern obtained using conventional CuK_α radiation (FIG. 4) having peaks at 7.7, 9.9, 16.5, 17.7, 18.3, 20.0, 21.9, 29.5 ± 0.2 degrees two-theta. The most characteristic peaks are at 16.5, 21.9, 29.5 ± 0.2 degrees two-theta.

Form XVI may be produced by maintaining Form XIV at from about 20° C to about 50°C, preferably about 22°C or room temperature, and preferably exposed to air. Preferably, Form XIV is maintained under these conditions for about three hours. Other conditions under which Form XVI is formed may be empirically determined. It is only possible to give methods which have so far been found suitable for producing it.

The present invention further provides a hydrated form of atorvastatin hemi-calcium that has been denominated Form XVII. Form XVII has been isolated as the immediate product obtained by precipitation from wet ethanol. As taught by U.S. Patent Application Publication No. 2992/0183378 (alternatively, see International Publication No. WO 01/36384 of PCT application number PCT/US00/31555), Form VIII can be prepared from a dispersion of Form V in a mixture of 96% ethanol/water at a temperature of about 70°C. By using this procedure in scales of at least 1 liter or more, the precipitated material, prior to being dried, is obtained in Form XVII.

Atorvastatin hemi-calcium Form XVII is characterized by a powder X-ray diffraction pattern obtained using conventional CuK_α radiation by typical X-Ray peaks at 19.1, 20.6, 21.4 and 23.6±0.2 degrees two-theta. Additional peaks are observed at 7.8, 9.5, 10.2, 18.2, 19.1, 25.3, 26.2, 30.1±0.2 degrees two-theta. Form XVII is also characterized by the typical X-Ray powder diffraction pattern of FIG. 5. Form XVII is distinguishable from Form VIII (the material obtained by complete drying of material obtained by precipitation from 96% ethanol/4% water) by the peak pattern in the range of 9-10, 18-25

degrees two-theta. In particular, Form VIII exhibits two strong peaks at 19.2 and 20.0±0.2 degrees 2θ, while Form XVII has one strong peak at 19.1±0.2 degrees 2θ, but no comparably strong peak at 20±0.2 degrees 2θ.

Atorvastatin hemi-calcium Form XVII may be produced by suspending atorvastatin hemi-calcium Form V in a mixture of 96% ethanol and 4% water (v/v) and heating to about 78-80°C, followed by cooling. Form XVII can be isolated immediately after the material starts to precipitate in the mixture at reflux temperature, or after all the material is precipitated, after the material is cooled down to room temperature, or after all the solid is isolated from the mother liquor (for instance by filtration). Although there may be other ways to obtain Form XVII, the best way presently known is to suspend atorvastatin hemi-calcium Form V in at least about 500 milliliters or more of a mixture of about 96% ethanol and about 4% water (v/v) and refluxing the suspension, followed by cooling. The solids are then recovered by conventional means such as filtering or decanting as Form XVII. Additional experimental details are provided in Example 6. The volume of the reactor should be at least about 1 liter.

The present invention also provides novel processes for preparing known forms of atorvastatin hemi-calcium.

Atorvastatin hemi-calcium Form I may be produced by heating Form XIV to about 50° C or above, preferably about 65°C. Preferably, Form XIV is maintained at elevated temperature for about 15 hours.

It will be appreciated from the foregoing disclosure that conventional drying of Form XVII transforms it into Form VIII. By conventional drying it is meant the methods of drying routinely used by those skilled in the art in the pharmaceutical industry. Any drying type of equipment conventionally used in the pharmaceutical industry is suitable for this purpose. A drying temperature in the range of about 40-70°C (in temperature steps or in one temperature only) is preferred. The amount of time required to convert Form XVII to Form VIII depends on the quantity of material employed. Vacuum may be preferably used to convert Form XVII to Form VIII by drying. Preparation of Form VIII also may be achieved by drying Form XVII at temperatures lower than 40°C, down to room temperature.

It has been found that atorvastatin hemi-calcium Form IX can be prepared by suspending Form V in a mixture of 50% 1-butanol and 50% of another organic solvent(s) like acetone, 2-propanol, tetrahydrofuran, 1-propanol and methyl *t*-butyl ether. The mixture is used in an amount of about 20 milliliters per gram of Form V. The suspension is heated to reflux temperature for about 16 hours, after which time Form V is transformed into Form IX, which can then be recovered from the suspension by conventional means.

Atorvastatin hemi-calcium Forms IXa, XIV, XVI and XVII are useful for reducing the plasma low density lipoprotein level of a patient suffering from or susceptible to hypercholesterolemia. For this purpose, it will typically be administered to human patients in a unit dose of from about 0.5 mg to about 100 mg. For most patients, a dose of from about 2.5 to about 80 mg per day, more particularly from about 2.5 to about 20 mg per day, causes a lowering of the plasma low density lipoprotein level in human patients. Whether such lowering is sufficient or whether the dose or dose frequency should be increased is a determination that is within the skill level of appropriately trained medical personnel.

A further aspect of the present invention is a pharmaceutical composition and dosage form containing the novel forms of atorvastatin hemi-calcium.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising novel Forms IXa, XIV, XVI and XVII of atorvastatin hemi-calcium. In addition, Forms IXa, XIV, XVI and XVII solid compositions that are contemplated by the present invention may further include diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes.

Excipients that also may be present in a solid composition of Forms IXa, XIV, XVI and XVII atorvastatin hemi-calcium further include disintegrants like sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The Dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and losenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of atorvastatin hemi-calcium whereupon the properties that distinguish the solid forms of atorvastatin hemi-calcium are lost. However, the use of the novel forms to prepare such solutions (e.g. so as to deliver, in addition to atorvastatin, a solvate to said solution in a certain ratio with a solvate) is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention

typically contain from 0.5 to 100 mg of the novel atorvastatin hemi-calcium Forms IXa, XIV, XVI and XVII or mixtures thereof with each other or other forms of atorvastatin hemi-calcium. More usually, the combined weight of the atorvastatin hemi-calcium forms of a unit dosage are from 2.5 mg. to 80 mg.

Having thus described the various aspects of the present invention, the following examples are provided to illustrate specific embodiments of the present invention. They are not intended to be limiting in any way.

EXAMPLES

(Preparation of Atorvastatin Hemi-Calcium Form IXa)

Example 1

Atorvastatin hemi-calcium salt Form V (5 g) was suspended in a mixture of 1-butanol (90ml) and water (10ml) at reflux temperature (85°C) for 16 hours. The mixture was then cooled to room temperature and then to 0°C using an ice-bath. The product was isolated by filtration and dried at 65°C in a vacuum oven for 24 hours to give 4.73g (95%) of Atorvastatin hemi-calcium crystalline Form IXa.

Example 2

Atorvastatin hemi-calcium salt Form V (5 g) was suspended in a mixture of 1-butanol (10ml) and water (90ml) at reflux temperature for 16 hours. The mixture was then cooled to room temperature and then to 0°C using an ice-bath. The product was isolated by filtration and dried at 65°C in a vacuum oven for 24 hours to give atorvastatin hemi-calcium crystalline Form IXa.

(Preparation of Atorvastatin Hemi-Calcium Form XIV)

Example 3

Atorvastatin hemi-calcium Form V (1 g) was introduced into a 500 ml beaker. Water (240 ml) was added. The suspension was mixed for 5 hours. A fine suspension appeared. It was left standing undisturbed for three days. After three days white flakes formed in the suspension. The suspension was then filtered and analyzed by XRD as is. The resulting form is novel atorvastatin hemi-calcium Form XIV.

(Preparation of Atorvastatin Hemi-Calcium Form XVI)

Example 4

A small aliquot of form XIV was exposed to the air at room temperature for three hours, and then analyzed by XRD. The resulting form is Form XVI.

(Preparation of Atorvastatin Hemi-Calcium Form XVII)

Example 5

Wet Atoravstatin hemi-calcium salt Form V (53 g) was added to a hot solution (about 70°C) of ethanol (about 485 ml). The resulting quantity of water in ethanol should be about 4%. The mixture was refluxed for about 2 hours. The mixture was cooled to 15-20 degrees. The solid was filtered, washed with ethanol 96%. The material was then analysed by X-Ray powder diffraction and found to contain Form XVII. Conventional drying (40-70) degrees produced atorvastatin hemi-calcium Form VIII.

Example 6

About 20 kg of Atorvastatin hemi-calcium Form V was added to a hot solution (about 70°C) of ethanol (about 600 liters). The resulting quantity of water in ethanol should be about 4% , and it is adjusted according to the initial moisture level of Form V. The mixture was refluxed for about 2.5 hours. The mixture was cooled to 15-20°C and stirred at this temperature for at least 3 hours. The solid was filtered, washed with 96% ethanol. The material was then analyzed by powder X-Ray diffraction and found to contain form XVII. Conventional drying at 40-70°C produced atorvastatin hemi-calcium form VIII.

(Preparation of Atorvastatin Hemi-Calcium Form IX)

Example 7

Atorvastatin hemi-calcium salt Form V (1 g) in 1-BuOH (10ml) and EtOH (10ml) was heated to reflux for 1 h. The mixture was then cooled to room temperature and stirred at this temperature for additional 16 hrs. Filtration and drying at 65°C for 24 hrs gave

0.98g (98%) of atorvastatin hemi-calcium Form IX.

Example 8

Atorvastatin hemi-calcium salt Form V (5 g) was suspended in a mixture of 1-butanol (50ml) and Acetone (50ml) at reflux temperature (71°C) for 17 hours. The mixture was then cooled to room temperature and then to 0°C using an ice-bath. The product was isolated by filtration and dried at 65°C in a vacuum oven for 24 hours to give 4.6g (93%) of Atorvastatin hemi-calcium salt Form IX.

Example 9

Atorvastatin hemi-calcium salt Form V (5 g) was suspended in a mixture of 1-butanol (50ml) and IPA (50ml) at reflux temperature (91.5°C) for 15 hours. The mixture was then cooled to room temperature and then to 0°C using an ice-bath. The product was isolated by filtration and dried at 65°C in a vacuum oven for 24 hours to give 4.7g (94%) of Atorvastatin hemi-calcium salt Form IX.

Example 10

Atorvastatin hemi-calcium salt Form V (5 g) was suspended in a mixture of 1-butanol (50ml) and THF (50ml) at reflux temperature (80°C) for 15 hours. The mixture was then cooled to room temperature and then to 0°C using an ice-bath. The product was isolated by filtration and dried at 65°C in a vacuum oven for 24 hours to give 2.4g (48%) of Atorvastatin hemi-calcium salt Form IX.

Example 11

Atorvastatin hemi-calcium salt Form V (5 g) was suspended in a mixture of 1-butanol (50ml) and 1-propanol (50ml) at reflux temperature (95°C) for 16 hours. The mixture was then cooled to room temperature and then to 0°C using an ice-bath. The product was isolated by filtration and dried at 65°C in a vacuum oven for 24 hours to give 4.8g (96%) of Atorvastatin hemi-calcium salt Form IX.

Example 12

Atorvastatin hemi-calcium salt Form V (5 g) was suspended in a mixture of 1-butanol (50ml) and MTBE (50ml) at reflux temperature (73°C) for 16 hours. The mixture was then cooled to room temperature and then to 0°C using an ice-bath. The product was isolated by filtration and dried at 65°C in a vacuum oven for 24 hours to give 4.8g (97%) of Atorvastatin hemi-calcium salt Form IX.

Having thus described the invention with reference to particular preferred embodiments and illustrated it with examples, those in the art may appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as defined by the claims which follow.

CLAIMS

We Claim:

1. Solid crystalline atorvastatin hemi-calcium and solvates thereof characterized by a powder X-ray diffraction pattern having peaks at 9.3 and 9.5±0.2 degrees two-theta.

2. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 1 further characterized by peaks in the powder X-ray diffraction pattern at 15.7, 20.5, 21.1, 22.8, 23.8, 24.0, 25.3, 26.4, 26.8, 27.2, 29.2 and 31.6 degrees two-theta.

3. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 1 further characterized by a powder X-ray diffraction pattern generated using CuK_{α} radiation substantially as depicted in figure 2.

4. A process for preparing atorvastatin hemi-calcium having at least one characteristic of Form IXa comprising the steps of:
   a) suspending atorvastatin hemi-calcium Form V in a mixture selected from the group consisting of mixtures from about 85% to about 95% 1-butanol and from about 5% to about 15% water and mixtures of from about 5% to about 15% 1-butanol and from about 85% to about 95% water for a period of time sufficient to convert Form V to the atorvastatin hemi-calcium having at least one characteristic of Form IXa, and
   b) recovering solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form IXa from the suspension.

5. The process of claim 4 wherein the mixture is about 90% 1-butanol and about 10% water on a volume basis.

6. The process of claim 4 wherein the mixture is about 10% 1-butanol and about 90% water on a volume basis.

7. The process of claim 4 wherein the mixture is present in an amount of at least about 20 milliliters per gram of atorvastatin hemi-calcium Form V.

8. The process of claim 4 wherein the suspension is heated to an elevated temperature before recovering the solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form IXa from the suspension.

9. The process of claim 8 wherein the elevated temperature is about the reflux temperature of the mixture.

10. The process of claim 9 wherein the reflux temperature is about 85°C.

11. The process of claim 4 wherein the time sufficient to convert Form V to the solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form IXa is about 16 hours or less.

12. The process of claim 4 wherein the Form V is impure and the solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form IXa is more pure than the Form V by about 50% or more.

13. Solid crystalline atorvastatin hemi-calcium and solvates thereof having at least one characteristic of Form IXa prepared by a process comprising the steps of:
   a) suspending atorvastatin hemi-calcium Form V in a mixture selected from the group consisting of mixtures from about 85% to about 95% 1-butanol and from about 5% to about 15% water and mixtures of from about 5% to about 15% 1-butanol and from about 85% to about 95% water for a period of time sufficient to convert Form V to the atorvastatin hemi-calcium having at least one characteristic of Form IXa, and
   b) recovering solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form IXa from the suspension.

14. Solid crystalline and highly pure atorvastatin hemi-calcium and solvates thereof having at least one characteristic of Form IX prepared by a process comprising the steps of:
    a) suspending atorvastatin hemi-calcium Form V in a mixture of 90% 1-butanol and 10% water on a volume basis for a period of time sufficient to convert Form V to the atorvastatin hemi-calcium having at least one characteristic of Form IXa, and
    b) recovering solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form IXa from the suspension in 99.3% or greater chemical purity as determined by high performance liquid chromatographic separation of and quantitation by UV absorption at 254 nanometers.

15. Solid crystalline atorvastatin hemi-calcium and solvates thereof characterized by a powder X-ray diffraction pattern having peaks at 7.6, 9.8, 16.5, 29.4 ± 0.2 degrees two-theta.

16. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 15 further characterized by peaks at 18.1, 20.0, 20.4, 21.9, 22.4 and 23.6± 0.2 degrees two-theta in its powder X-ray diffraction pattern.

17. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 15 further characterized by a powder X-ray diffraction pattern generated using CuK_{α} radiation substantially as depicted in figure 3.

18. A process for preparing solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form XIV and solvates thereof comprising:
    a) suspending atorvastatin hemi-calcium in water, and
    b) recovering the flakes from the suspension.

19. The process of claim 18 wherein the atorvastatin hemi-calcium that is suspended is

Form V.

20. The process of claim 18 wherein the converting occurs over about 5 days.

21. The process of claim 18 wherein a fine suspended solid is formed about two to about 10 hours after the atorvastatin hemi-calcium is suspended in water.

22. The process of claim 18 wherein the fine suspended solid converts into flakes over from about one to about five days.

23. The process of claim 22 wherein conversion of the fine suspended solid into flakes occurs over about five days.

24. Solid crystalline atorvastatin hemi-calcium and solvates thereof characterized by powder X-ray diffraction pattern having peaks at 16.5, 21.9, 29.5 ± 0.2 degrees two-theta.

25. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 24 further characterized by additional peaks at 7.7, 9.9, 16.5, 17.7, 18.3, 20.0, 21.9, 29.5 ± 0.2 degrees two-theta in the powder X-ray diffraction pattern.

26. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 24 further characterized by a powder X-ray diffraction pattern generated using CuK_{α} radiation substantially as depicted in figure 4.

27. A process for preparing solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form XVI and solvates thereof comprising:
   a) maintaining atorvastatin hemi-calcium Form XIV crystals at from about 20°C to about 50°C, and
   b) recovering the crystals as solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form XVI.

28. The process of claim 27 wherein the atorvastatin hemi-calcium is maintained at about 22°C.

29. The process of claim 27 wherein the atorvastatin hemi-calcium is exposed to air while being maintained.

30. Solid crystalline Atorvastatin hemi-calcium and solvates thereof characterized by a powder X-ray diffraction pattern having peaks at 19.1, 20.6, 21.4 and 23.6±0.2 degrees two-theta.

31. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 30 further characterized by additional peaks at 7.8, 9.5, 10.2, 18.2, 19.1, 25.3, 26.2, 30.1±0.2 degrees two-theta in the powder X-ray diffraction pattern.

32. The solid crystalline atorvastatin hemi-calcium and solvates thereof of claim 30 further characterized by a powder X-ray diffraction pattern generated using CuK_{α} radiation substantially as depicted in figure 5.

33. A process for preparing solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form XVII and solvates thereof comprising:
    a) suspending atorvastatin hemi-calcium Form V in a mixture of about 96% ethanol and about 4% water,
    b) heating the suspension,
    c) cooling the suspension, and
    d) recovering solid atorvastatin hemi-calcium from the suspension having at least one characteristic of Form XVII.

34. The process of claim 33 wherein the mixture is used in an amount of at least about 500 ml.

35. The process of claim 33 wherein the suspension is heated to about 78-80°C.

36. A pharmaceutical composition comprising atorvastatin hemi-calcium selected from the group consisting of Form IXa, XIV, XVI and XVII or a mixture thereof and a pharmaceutically acceptable carrier.

37. Use of atorvastatin Form IXa, XIV, XVI and XVII or mixtures thereof, to prepare a pharmaceutical dosage form.

38. A pharmaceutical dosage form comprising atorvastatin hemi-calcium Form IXa, XIV, XVI, XVII or mixtures thereof.

39. A method of reducing the plasma low density lipoprotein level of a patient suffering from or susceptible to hypercholesterolemia by administering to the patient the pharmaceutical dosage form of claim 38.

40. A process for preparing solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form I and solvates thereof comprising:
    a) heating crystals of atorvastatin hemi-calcium Form XIV to about 50°C or above, and
    b) recovering the crystals as solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form I.

41. The process of claim 40 wherein the atorvastatin hemi-calcium Form XIV is heated to about 65°C.

42. A process for preparing solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form VIII comprising:
    a) providing atorvastatin hemi-calcium Form XVII,
    b) drying the Form XVII to transform it into atorvastatin hemi-calcium having at least one characteristic of Form VIII, and

c) recovering the atorvastatin having at least one characteristic of Form VIII.

43. The process of claim 42 wherein drying includes heating the Form XVII to an elevated temperature.

44. The process of claim 43 wherein the elevated temperature is from about 40°C to about 70°C.

45. A process for preparing solid crystalline atorvastatin hemi-calcium having at least one characteristic of Form IX comprising:

a) suspending atorvastatin hemi-calcium Form V in a mixture of approximately 50% 1-butanol and 50% another organic diluent, and

b) recovering atorvastatin hemi-calcium having at least one characteristic of Form IX from the suspension.

46. The process of claim 45 wherein the organic diluent is selected from the group consisting of acetone, 2-propanol, tetrahydrofuran, 1-propanol and methyl *t*-butyl ether.

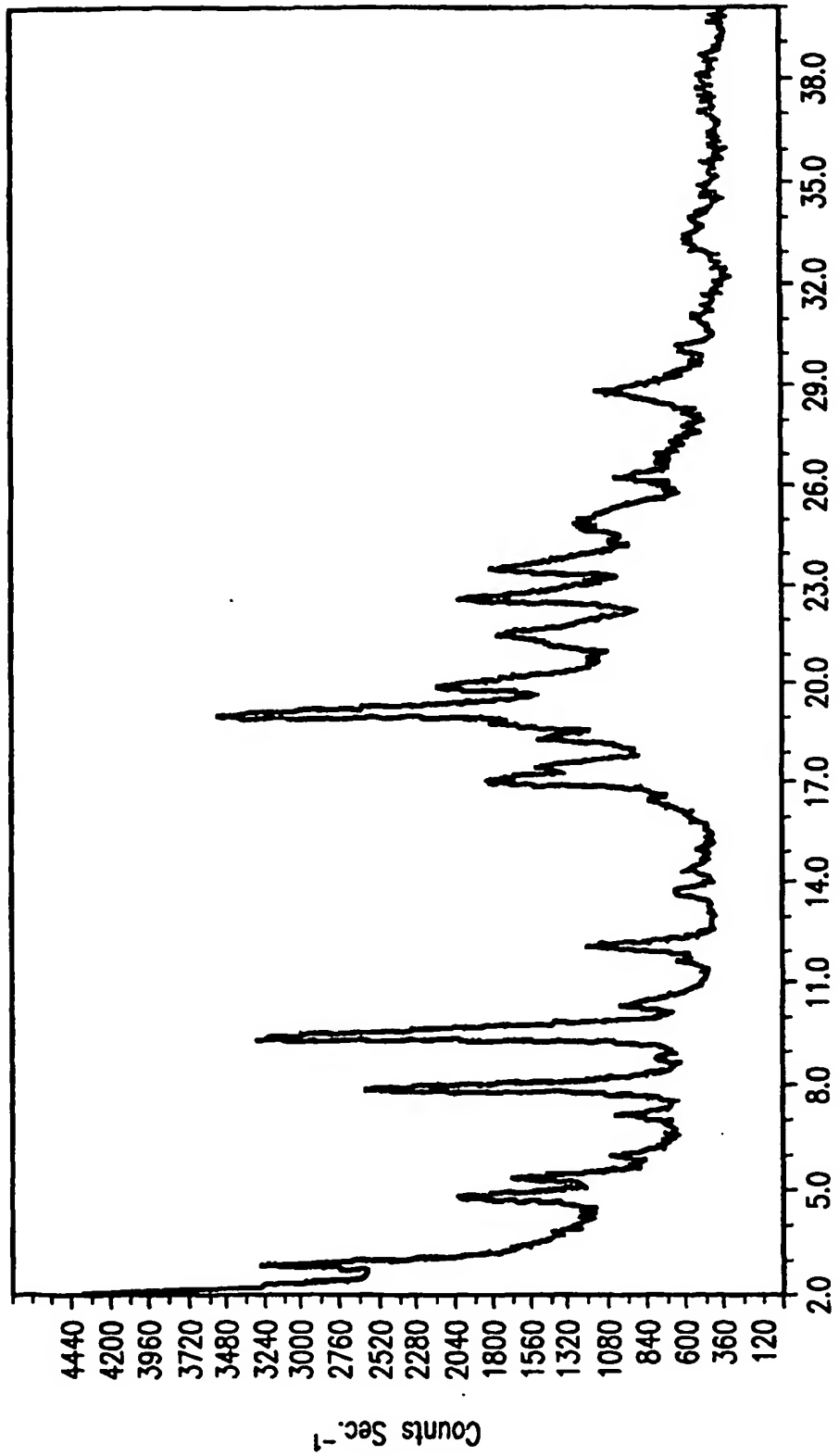

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Fig. 1

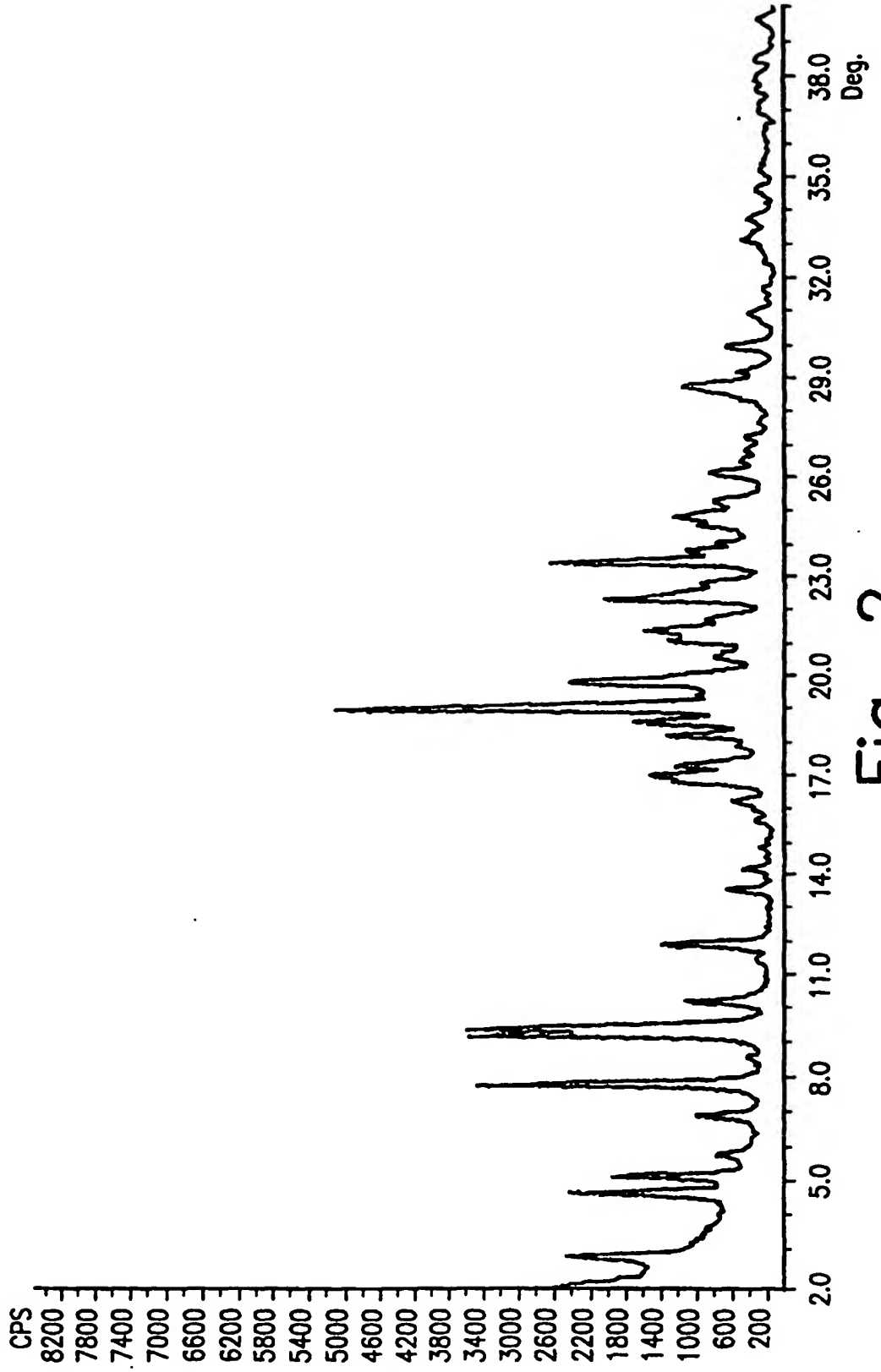
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Fig. 2

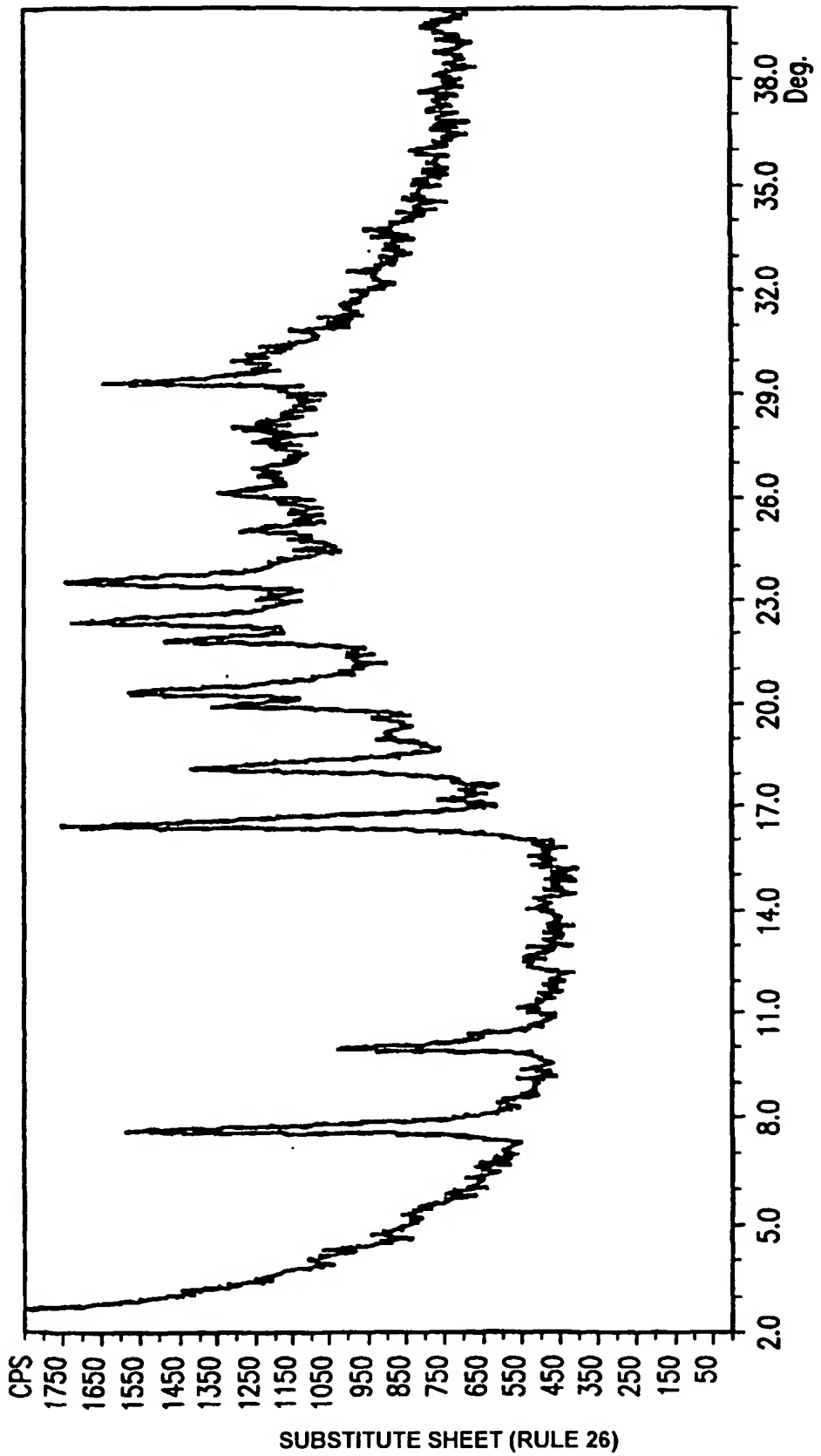
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Fig. 3

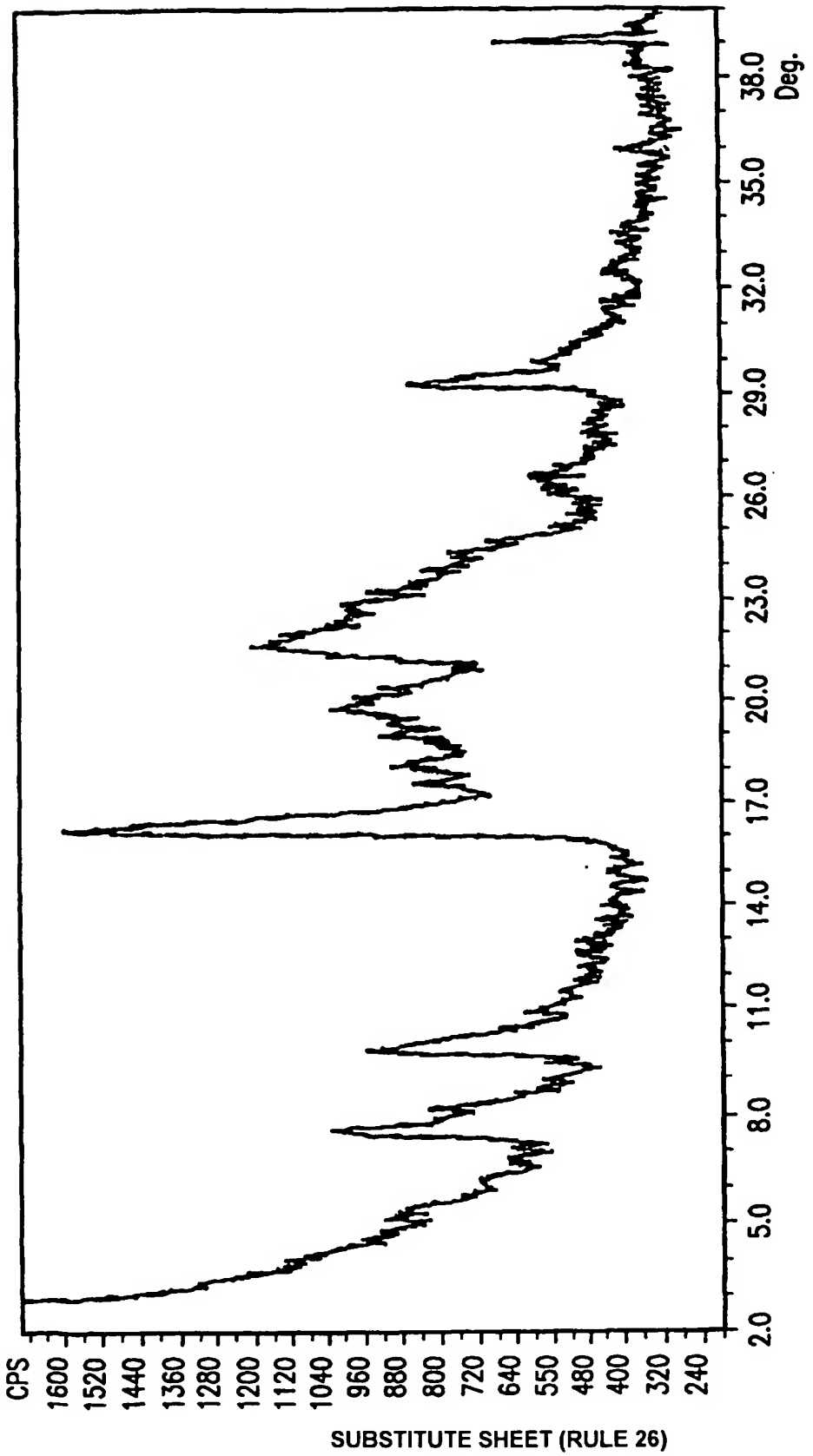
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Fig. 4

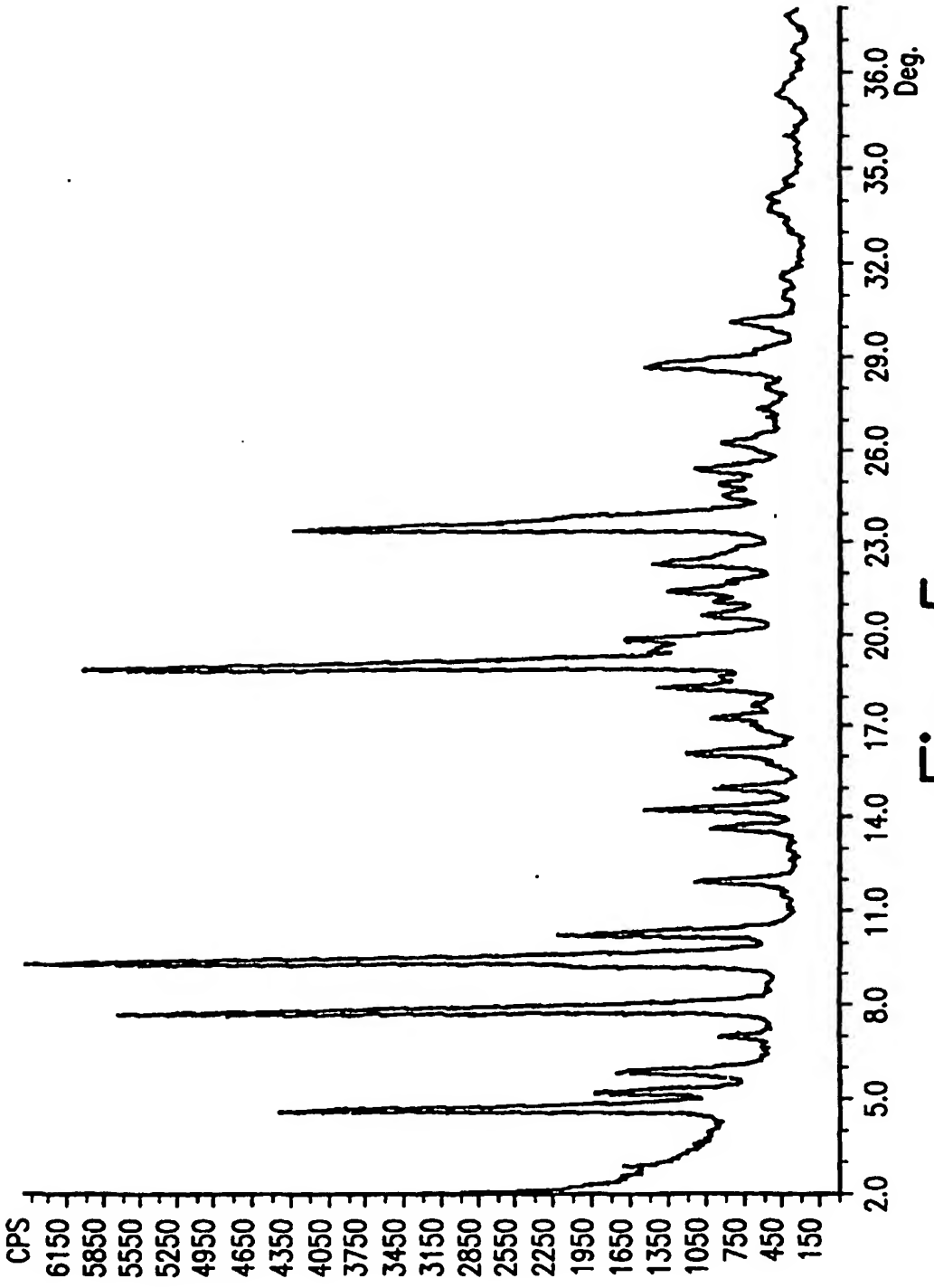
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Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/05384

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 207/327
US CL : 548/537
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/537

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,087,511 A (LIN et al) 11 July 2000 (11.07.2000), column 2, lines 16-22.	4-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
16 May 2003 (16.05.2003)

Date of mailing of the international search report
01 JUL 2003

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Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/05384

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1-3 and 13-46
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/05384

Continuation of Item 4 of the first sheet:
The title is too long, PCT Rule 4.3 suggested follows: "Novel Crystal Forms of Atorvastatin Hemi-Calcium"

Continuation of Box I Reason 2:
In these claims, the virtual unlimited scope of the subject matter (e.g. reactants and reaction conditions) and where present, the various limitations of the compounds, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same.